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Clinical Pharmacokinetics

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In Chapter 1 the basic principles of pharmacokinetics were presented. Clinical pharmacokinetics is the discipline in which basic pharmacokinetic principles are applied to the development of rational dosage regimens. In this chapter the concepts of pharmacokinetics are placed into perspective with the development of individualized drug dosage regimens. The clinical significance of the processes of drug absorption, distribution, elimination, and influence of disease states on these processes are emphasized. Examples will be given of the ways pharmacokinetic principles can be applied in the calculation and adjustment of dosage regimens designed to fit the pharmacokinetic and pharmacodynamic properties of drugs and specific disease states that alter drug disposition. The principles of therapeutic drug monitoring and the rational use of this clinical science in the management of patients also are discussed.

An individualized dosage regimen for a patient involves a decision about the dose or amount of drug to be administered, interval between doses, route of administration, and patient factors that may change during the course of drug administration. The latter implies that there is a plan for monitoring the therapeutic and adverse effects of the drug. Decisions about drug dose, dosage intervals, and route of administration are based on the clinical knowledge of the disease being treated, efficacy of the drug in treating the disease, and absorption, distribution, and elimination of the drug.

Absorption

Drugs are administered by a variety of routes including intravenous, intramuscular, inhalation, oral, rectal, vaginal, and topical application to the skin. The choice of the route depends on the many patient- and drug-related factors discussed in Chapter 11. In practical terms, the important considerations in this choice include the systemic availability of a particular dosage form, rate, and extent of drug absorption, and patient convenience.

Oral Route This route is chosen most frequently because of ease of administration and patient acceptance. However, the number of variables involved in the absorption of drugs from the stomach and small intestine make the oral route of administration quite complex.

Plasma concentration-time curves will reflect some of these complexities. One of these is the relative rates of absorption of different preparations of the same drug (Fig 1), in which preparation *A* represents a simple, rapidly absorbed preparation of a drug, *B* is a more slowly absorbed derivative of the same base. The bioavailabilities of *A* and *B* are identical and *C* is the same compound as *B* but in a dosage form that is only 50% as bioavailable as *B*. *A* is absorbed rapidly, the k_a for *A* is greater than for *B* or *C*, and the peak level is in the therapeutic plasma concentration range.

The advantage of such a preparation is that a pharmacodynamic response can be expected to occur quickly, provided the response is related to plasma concentration. To appreciate the clinical relevance of the situation, consider *A* to be quinidine sulfate, a cardiac arrhythmic drug. For quinidine sulfate, the absorption rate constant (k_a) is large in relation to the elimination rate constant (k), and the peak concentration occurs relatively early, at 1 to 2 hours. Therapeutic absorption is important in clinical situations in which some degree of urgency exists.

It may be desirable in the initiation of therapy of ominous ventricular premature contractions to use a preparation with the characteristics of quinidine sulfate. The half-life of quinidine is 6 to 8 hours, so that frequent doses, every 4 hours, are necessary to maintain effective blood concentrations of the drug. The short half-life can be an advantage since steady-state concentrations of quinidine are achieved within 24 hours (plateau principle). Therefore, one can decide within a day whether quinidine will be useful in suppressing the ventricular premature contractions. However, the fact that a dose must be administered every 4 to 6 hours to maintain therapeutic plasma concentrations is somewhat of a disadvantage in that it is inconvenient and may result in noncompliance.

Preparation *B*, with its slower rate of absorption, reaches a lower peak concentration at a considerably later time even though given in the same dose. There are clinical consequences of this. For example, if *B* was the sustained-release form of quinidine gluconate, it would be less desirable than quinidine sulfate for the initiation of drug therapy, where a rapid therapeutic response is needed. Because of its prolonged absorption, this preparation commonly is administered every 8 to 12 hours. This is so because the slower rate of absorption enables the dose to be increased commensurate with a longer dose-interval without peak concentrations that rise into the toxic range.

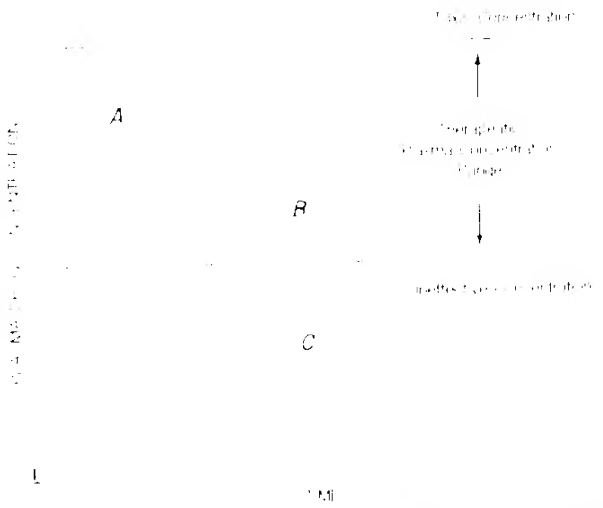

Fig 1. Plasma drug concentration-time curves of three preparations of the same drug. *A* is rapidly and completely absorbed. *B* is not absorbed as rapidly as *A* (e.g., 100 mg available). *C* has the same time to peak concentration as *B* but is only 50% as available. (Courtesy, adapted, Brodie.)

When treating a patient in which a rapid (but not immediate) effect is required (as with asymptomatic ventricular premature contractions), it is advisable to use a dosage form to initiate therapy that is absorbed rapidly and completely. Once the drug is shown to be effective in a particular patient, the dosage form can be changed to one with characteristics similar to *B*, so that less-frequent dosing is required and patient compliance is improved.

The preparation represented by *C in the same dose* as *A* or *B* is probably not an acceptable way to administer this drug. The total amount of drug *C* that is absorbed is only half of that of *B* (area-under-the-plasma concentrations-time curve, AUC, for *C* is half of the AUC for *B*). Thus, it would require twice the dose to attain blood levels equivalent to *A* or *B*.

The treatment of asthma with theophylline is an example in which a rapidly absorbed dosage form is used to initiate therapy and a prolonged-release dosage form is used for maintenance therapy. When a patient has an acute asthma attack or worsening bronchitis that requires bronchodilator therapy, it is advisable to use the theophylline-ethylenediamine complex (aminophylline). This dosage form can be administered either intravenously or orally; the former should be used to initiate treatment in the acute asthmatic patient who requires prompt therapy, so that neither a delay in achieving therapeutic plasma concentrations nor bioavailability are factors in the initial therapeutic response.

Following the administration of an aminophylline loading dose (see under *Distribution*, page 743), the drug should be given by continuous intravenous infusion until the acute symptoms have subsided, which may take 24 to 72 hours. In the patient with less-severe symptoms, aminophylline can be administered orally four times a day. Once the patient's condition has improved and an effective dose of theophylline has been established, then it may be possible to switch the patient to a prolonged-release formulation for maintenance therapy.

The absorption and bioavailability of Theodur and Sustaire, two sustained-release theophylline preparations, permit 12-hour dosing intervals; Slo-Phyllin Gyrocaps should be given every 8 hours. The total daily dose of theophylline that was required during intravenous aminophylline administration is divided into smaller oral doses given at intervals appropriate for the characteristic of the preparation or dosage form used.

It is important to keep in mind that the absorption and plasma-time curve characteristics for these preparations usually have been established in healthy volunteers or asthmatic patients without other illnesses. Patients who eliminate theophylline rapidly (ie, smokers) may have increased dosage requirements, and the dosage interval may have to be shortened to avoid recurrent asthmatic symptoms between doses.

Prolonged-release dosage forms have the additional advantage that fluctuations in blood levels of the drug will be less than with rapidly absorbed dosage forms. There is evidence for some drugs that the reduction in rapidly changing blood levels may improve efficacy and decrease adverse effects. For example, the dose of fentanyl or ketamine required to maintain anesthesia was reduced by nearly 50% when the drugs were given by continuous infusion rather than by intermittent bolus.[1]

This reduced dose also resulted in more rapid recovery with less-prolonged sedation. These findings suggest that a reduction of fluctuation in the plasma concentrations will reduce total dosage requirement. If such a reduction in plasma concentration fluctuation also applies to oral prolonged-release dosage forms, it would provide a distinct advantage for their use.

The bioavailability of a particular drug product, by any route of administration, can be determined by comparison of the AUC of a drug given by the route of interest with that of the same dose given intravenously (see Chapter 41). In the case of an orally administered drug, it is the ratio of the AUC after an oral dose to the AUC after an intravenous dose. The decreased bioavailability of an oral dose may be due to poor gastrointestinal absorption of the drug because it does not go completely into solution, as it may be degraded in the gastrointestinal lumen, or it does not pass across the intestinal mucosa. Furthermore, in order to reach the general circulation, drugs taken orally must pass through the wall of the gastrointestinal tract and then to the liver via the portal vein. Thus, drug metabolism may occur in the gut wall or in the liver and severely limit the delivery of parent drug to the general circulation.

If the extraction of the drug by the liver is efficient, oral administration results in low bioavailability and sometimes limited pharmacological effect. This is commonly referred to as *first-pass metabolism* (presystemic metabolism). Table 1 lists some of the drugs known to exhibit first-pass metabolism. Because their extraction is high and their rate of metabolism great, the rate-limiting step in the clearance of drugs in Table 1 is liver blood flow. The metabolism of these drugs can be referred to as *flow-limited*. The clinical significance of changes in liver blood flow on drug bioavailability will be discussed under *Drug Therapy in Hepatic Disease*.

Different dosage forms of the same drug may have different systemic bioavailabilities. The ratio of the AUC for one dosage form to that of another dosage form is termed the *relative bioavailability*. A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases. Furthermore, a drug in one dosage form made by one manufacturer may have a different bioavailability from that of another manufacturer.

With drugs for which bioavailability varies significantly from product to product, if one product initially has been efficacious, it is advisable to continue with that product. If for economical or other reasons the product must be changed to that manufactured by a different company, it is wise to observe the patient carefully for a possible change in clinical response indicative of a change in bioavailability. Products designed for prolonged release sometimes have a low bioavailability. However, this may not be a problem during maintenance therapy so long as therapeutic serum concentrations are achieved consistently.

The presence of food in the stomach or intestine can have a profound influence on the rate and extent (bioavailability) of drug absorption. Initial absorption studies for a new drug, performed in healthy volunteers, commonly include fasting and nonfasting conditions. Therefore, in general, and for controlled diets, the effect that food may have on drug absorption may be known when a drug is introduced into the market. Unfortunately, food-drug interactions are not consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium or magnesium.

The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach also has been shown to

Table 1—Drugs that Exhibit First-Pass Metabolism

Acetylsalicylic acid	Morphine
Alprenolol	Nitroglycerin
Amitriptyline	Nortriptyline
Desipramine	Pentazocine
Dopamine	Prazosin
Imipramine	Propoxyphene
Isoproterenol	Propranolol
Lidocaine	Salicylamide
Meperidine	Verapamil
Metoprolol	